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General Information

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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_eim_ravi.pdf

https://yoda.yale.edu/system/files/yoda_coi_-_uniti_eim_aruljothy.pdf

https://yoda.yale.edu/system/files/yoda_coi_narula_0.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. [NCT01369329 - CTO1275CRD3001 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy \(UNITI-1\)](#)
2. [NCT01369342 - CTO1275CRD3002 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease \(UNITI-2\)](#)
3. [NCT01369355 - CTO1275CRD3003 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Effectiveness of Ustekinumab on Arthritis/Arthralgia in Crohn's Disease: post hoc Analysis of UNITI

Narrative Summary:

Ustekinumab (UST) is a monoclonal antibody that targets the standard p40 subunit of the cytokines IL-12 and IL-23 (IL12/23p40), which are involved in the pathogenesis of Crohn's disease (CD). UST was shown to be effective in inducing and maintaining clinical remission in CD patients with moderate to severe CD (6,7,8). UST has produced consistent clinical efficacy in treatment of psoriatic arthritis (1-3). However, there are no studies that have assessed the effectiveness of in CD in remission of extra-intestinal manifestations, specifically arthritis and arthralgia. This post hoc study aims to evaluate UST efficacy in treatment of arthritis and arthralgia in moderate-severe CD patients.

Scientific Abstract:

Background & Rationale: Ustekinumab (UST) is a monoclonal antibody that targets the standard p40 subunit of the cytokines IL-12/23 and has been shown to be effective in inducing and maintaining clinical remission in moderate-severe CD (6,7,8). UST has shown to have clinical efficacy in treatment of psoriatic arthritis (1-3). However, there are no studies that have assessed the effectiveness of in CD in remission of arthritis and arthralgia.

Objective: This post hoc analysis aims to evaluate the efficacy of UST in treatment of arthritis and arthralgia in moderate-severe CD patients.

Study Design: UNITI-1/ 2 trials were multi-centre, double blinded, placebo-controlled trials that randomized patients to ustekinumab or placebo. The induction trials were 8 weeks, which were followed by the 44-week IM-UNITI trial for patients who had an initial response. We will be conducting a post-hoc analysis.

Participants: Adult patients with moderate-to-severe CD [defined as a Crohn's Disease Activity Index (CDAI) score 220-450) who were eligible for UNITI-1 and UNITI-2.

Main Outcome Measure(s): The presence (scored 20 on CDAI) or absence (scored 0 on CDAI) of arthritis/arthralgia, measured at baseline, weeks 3, 6, 8 and 44. The secondary outcomes will evaluate the presence (scored 20 on CDAI) or absence (scored 0 on CDAI) of other extra-intestinal manifestations.

Statistical Analysis: Univariate and multivariate regression analyses will be performed to assess for the association of arthritis/arthralgia and efficacy outcomes of clinical remission and mucosal healing.

Brief Project Background and Statement of Project Significance:

Ustekinumab (UST) is a monoclonal antibody that targets the standard p40 subunit of the cytokines IL-12 and IL-23 (IL12/23p40), which are involved in the pathogenesis of Crohn's disease (CD). UST was shown to be effective in inducing and maintaining clinical remission in CD patients with moderate to severe CD (6,7,8). UST has produced consistent and clinical efficacy in treatment of psoriatic arthritis (1-3). However, to our knowledge, there are no studies that have assessed the effectiveness of UST in CD in remission of extra-intestinal manifestations, specifically arthritis and arthralgia. This has clinical implications in moderate-severe CD as it establishes what characteristics of disease activity (extent, severity, mucosal healing) are correlated or associated with the presence of extra-intestinal manifestations of IBD.

Specific Aims of the Project:

This post hoc analysis of moderate-severe CD patients from UNITI-1 (ClinicalTrials.gov number: NCT01369329), UNITI-2 (ClinicalTrials.gov number: NCT01369342), and IM-UNITI (ClinicalTrials.gov number: NCT01369355) aim to evaluate the efficacy of UST in treatment of arthritis and arthralgia in moderate-severe CD.

Our hypothesis is that UST is effective in remission of baseline arthritis or arthralgia in patients with moderate-severe CD. The effectiveness of UST to induce remission and maintain the absence of arthritis/arthralgia and other extra-intestinal manifestations (iritis, uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula/abscess, other fistula, and fever over 100°F (37.8°C) during the previous 7 days will be performed).

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Confirm or validate previously conducted research on treatment effectiveness

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

The study will utilize data from the Yale University Open Data Access (YODA) Project. Participant-level data will be required for the following trials: UNITI-1 (ClinicalTrials.gov number: NCT01369329), UNITI-2 (ClinicalTrials.gov number: NCT01369342), and IM-UNITI (ClinicalTrials.gov number: NCT01369355). UNITI-1 and UNITI-2 were two multicentre, double-blinded, placebo-controlled trials that randomized patients to UST or placebo in CD. These induction trials were 8 weeks in duration and were followed with a 44-week follow-up period in the IM-UNITI trial for patients who had an initial response. Inclusion Criteria were as follows: (a) ≥18 years of age, (b) CD for a minimum duration of 3 months, (c) Moderate-to-severe CD (defined as a CDAI 220-450), (d) Nonresponse to anti-TNF therapy, treatment failure to immunomodulators and/or glucocorticoids, (3) Participants from UNITI-1/2 with an initial response and those in IM-UNITI. The exclusion criteria were as follows: (a) Bowel resection within 6 months, (b) Infliximab, adalimumab or certolizumab pegol ≥8 weeks before receiving study drug, (c) Ongoing chronic/recurrent infectious disease, (d) Prior IL-12/23 antagonist

Main Outcome Measure and how it will be categorized/defined for your study:

The CDAI is a tool consisting of eight variables used to assess the quality of life of patients with CD, and was the primary measurement of disease activity response to UST (5). UNITI defined clinical response as a decrease in CDAI score of ≥100 points from week 0 of induction or clinical remission. Furthermore, clinical remission was defined as a CDAI score <150. This scoring system included extra-intestinal manifestations of Crohn's disease as one of the 8 variables, which were the following: iritis, uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula/abscess, other fistula, and fever over 100°F (37.8°C) during the previous 7 days will be performed. UST efficacy assessments using the CDAI were measured at baseline, week 3, week 6 and 8 in the induction trials (UNITI-1 and 2). In the maintenance trial (IM-UNITI), CDAI was measured at week 44. The primary outcome of this post hoc analysis will be the presence (scored 20 on CDAI) or absence (scored 0 on CDAI) of arthritis/arthralgia, as measured by the CDAI at baseline, weeks 3, 6, 8 and 44. Only patients that had an initial response to UST from UNITI-1/2 will be included in the analysis.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

CD disease activity will be the main predictor, which will be measured with CRP levels (measured at weeks 0, 3,

and 8 during induction and at 4-weeks intervals during maintenance) , and fecal calprotectin levels (measured at weeks 0 and 6 during induction, and at weeks 8, 24, and 44 during maintenance).

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

The evaluation for the presence (scored 20 on CDAI) or absence (scored 0 on CDAI) of other extra-intestinal manifestations of CD such as iritis, uveitis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, anal fissure/fistula/abscess, other fistula, and fever over 100°F (37.8°C) during the previous 7 days will be performed.

Statistical Analysis Plan:

Descriptive statistics will be used to summarize baseline demographics and disease characteristics of CD patients. Continuous variables will be presented as means (and standard deviations [SD] or as medians and interquartile ranges [IQR] if the distribution is skewed). Categorical or binary variables will be presented as proportions or percentages. Univariate and multivariate regression analyses will be performed to assess for the association of the presence of arthritis/arthralgia and efficacy outcomes of clinical remission, clinical response and mucosal healing in UNITI-1/2 and IM-UNITI.

Approved investigators will be granted access to participant-level data sets provided by the YODA project via a remote, secure, password-protected data sharing platform. All work on the data will take place within the secure platform. Analyses with data provided by the YODA project will be conducted using the software available on the remote platform. The platform will be easily accessible to researchers, and ongoing system monitoring and support will be available. If needed, researchers will be able to upload additional data sets to the secure platform, if the researcher has the rights/license to do so.

Software Used:

STATA

Project Timeline:

Anticipated Project Start Date: To be started within the first week of database approval and acquisition in January 2020.

Analysis Completion Date: Research proposal to be finalized with data collection and analysis. Estimated date of completion will be March 2020.

Manuscript Draft Date: Manuscript draft estimated to be completed in April 2020.

Manuscript Submission Date: April 2020 – May 2020.

Any manuscripts, abstracts, posters, presentations, etc. will be shared with the YODA Project at the time of submission.

Dissemination Plan:

Anticipated products include abstracts, which will be published or shared during scientific meetings, including Canadian Digestive Diseases Week, Digestive Disease Week, and European Crohn's and Colitis Organisation. Additionally, a manuscript is expected to be completed for the research project and will be submitted for publication to relevant peer-reviewed journals. Potential journals for submission include Clinical Gastroenterology and Hepatology, Journal of Crohn's and Colitis, Inflammatory Bowel Diseases, and Digestive Diseases and Sciences. The dissemination of results, which may include but are not limited to abstracts, manuscripts, preprints, posters, and slide decks will be shared with the YODA Project at the time of submission. Target audiences include clinicians and researchers interested in the advancement of the inflammatory bowel disease diagnostics and management.

Bibliography:

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5. Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology*. 1994;106(2):287-96.